REMARKS

Missing enclosures

The Final Office Action notes the absence of enclosed BLAST reports that were supposed to be part of the Office Action Response of 7 February 2001. Applicants are surprised by this inadvertent omission since the BLAST reports were an integral part of the previous Office Action Response. The BLAST reports are enclosed with the instant Final Office Action Response. For the Examiner's convenience, the statements pertaining to these enclosures that originally appeared in the previous Office Action Response are reiterated below (see, for example, ***Applicants' invention***). Applicants believe that the results of these BLAST reports would convince one skilled in the art that PANEC are leukocyte-specific chemokines and earnestly request that they be taken into consideration despite their belated receipt in the PTO.

Status of claims and amendments

All previously filed claims were canceled and new claims 40-60 were added by the amendment in the Office Action Response of 7 February 2001. Applicants acknowledge the constructive election of claims 40-42, 46-47, and 52-54 and the withdrawal of claims 43-45, 48-51, and 55-60. However, Applicants note that claims 48-50 and 60 are drawn to methods of use of the polynucleotides of elected claims 40-42 and should be examined together, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants therefore request the examination of claims 48-50 upon indication of allowable subject matter in the instant application.

Claims 40 and 52-54 have been amended above to address rejections made in the Final Office Action (see below).

The title of the above identified application has been changed to "POLYNUCLEOTIDES ENCODING LEUKOCYTE-SPECIFIC CHEMOKINES EXPRESSED IN PANCREAS" to more accurately describe the subject matter and to address the comments in the Final Office Action at page 17-18.

The paragraph on page 6, lines 8-10, has been replaced to correct the missing reference to Table 6 in the specification. This amendment is responsive the comments in the Final Office Action at page 17.

Failure to comply with 37 C.F.R. §§ 1.821 through 1.825

The Final Office Action reiterated a request for a Substitute Sequence Listing in accordance with 37 C.F.R. §§ 1.821 through 1.825 (Office Action page 3). Upon inspection of the prosecution history of the instant application, Applicants have determined that a Substitute Sequence Listing in both paper form and computer-readable format was already submitted with the Office Action Response of 17 February 1995. A postcard indicates that this matter was received in the PTO. The Substitute Sequence Listing included the polypeptide sequences of MIP-1α, MIP-1β, RANTES, MCP-1, MCP-2, MCP-3, and a consensus sequence, in addition to the polypeptide and polynucleotide sequences of SEQ ID NO:1-4. However, the Substitute Sequence Listing did not correct the discrepancy between the polynucleotide length of SEQ ID NO:1 in Figure 1 and the original Sequence Listing (*i.e.,* 291 or 289 nucleotides).

Find enclosed a paper copy and disk containing a computer-readable version of a second Substitute Sequence Listing which indicates the correct polynucleotide sequence of SEQ ID NO:1, which is 291 nucleotides, as shown in Figure 1. Applicants believe the new Substitute Sequence Listing to be in compliance in with 37 C.F.R. §§ 1.821 through 1.825.

Applicants point out that the above referenced Office Action Response of 17 February 1995 also contained a number of other amendments to the instant specification and request entry of these amendments if they have not already been entered.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 40-42, 46-47, and 52-54 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Final Office Action, page 6). Specifically, the Final Office Action refers to the term "stringent" in the context of "stringent hybridization conditions" which is not explicitly described in the instant specification.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art. The term "stringent hybridization conditions" is well known to those skilled in the art. Since the description of the Southern blot in 1975 and the Northern blot in 1980 [Southern, E.M. (1975) J. Molec. Biol. 98:503-517; Thomas, P.S. (1980) Proc. Natl. Acad. Sci. USA 77:5201-5205; respectively (not enclosed)], the hybridization of nucleic acids has become a basic tool for the molecular biologist.

Hybridization conditions depend upon the length of the polynucleotides being hybridized and are typically dictated by the length of the probe. As a result, molecular biologists rarely report hybridization condition in terms of specific temperature. Also, since there are numerous hybridization buffers that work equally well but require different hybridization temperature to achieve the same result. For example, increasing formamide concentration require reduced hybridization temperatures). It is more useful to express hybridization conditions in terms of stringency. The term "stringent hybridization conditions" refers to conditions that are about 5°C below the melting temperature (Tm) of the expected DNA-DNA or RNA-DNA complex. This term is so common that is frequently used without further elaboration or definition. For example, U.S. Patent No. 6,261,836 (Cech, *et al.*) includes the following claim:

> 1. A synthetic or recombinant human telomerase reverse transcriptase (hTRT) protein, or a variant thereof, or a fragment thereof, wherein said variant is encoded by *a polynucleotide that hybridizes under stringent conditions* to a polynucleotide having a sequence complementary to SEO ID NO: 224, and wherein said hTRT protein, variant, or fragment has telmerase catalytic activity when complexed with a telomerase RNA. (Emphasis added.)

The term "stringent hybridization conditions" is not further defined in the Cech *et al.* specification nor is there a reference associated with the term. The term is understood by one skilled in the art and need not be further elaborated. Thus, in the case of the instant application, Applicant submit that one skilled in the art would immediately understand and recognize the meaning of the phrase "stringent hybridization conditions." For at least these reasons, Applicants request withdrawal of the rejection.

Written description rejection under 35 U.S.C. §112, first paragraph

The claims have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. Specifically, the Final Office Action rejects claims 40-42 and 46-47 because they allegedly encompass genomic sequences that are not adequately described in the specification. Claims 41-42 and 46-47 all depend from claim 40. This rejection is respectfully traversed.

Claim 40 recites polynucleotide sequences that encode the polypeptides in of parts (a) and (b) of the claim. The polynucleotides recited in parts (c-e) of claim 40 are presumably not at issue. Claim 40 does not contemplate genomic sequences. In humans and higher eukaryotes, genomic DNA contains numerous introns which must be spliced out of the corresponding mRNA prior to translation. Had Applicants intended that claim 40 encompass genomic polynucleotide sequences, the claim would have to have been substantially reworded to avoid any recitation of polypeptides that were potentially encoded by the claimed polynucleotides because one skilled in the art would immediately recognize that genomic polynucleotide sequences are not directly translated into proteins. Consequently, defining a genomic polynucleotide sequence by the polypeptide it ultimately encodes (as is the case in claim 40) would ignore mRNA processing steps that are fundamental to eukaryotic gene expression. One skilled in the art would simply not associate a genomic polynucleotide sequence with a polynucleotide sequence that was expressly defined as a sequence encoding a polypeptide.

Even if the literal claim language could, under certain circumstances, encompass an unspliced or incompletely spliced polynucleotide sequence with genomic content (which Applicants do not concede), there is likely no value in the translation product of the polynucleotide and no value in the polynucleotide itself. For example, if an intron fortuitously contained an open reading frame which was also in frame with both flanking exons, the hypothetical polypeptide encoded by the polynucleotide sequence would be distinct from SEQ ID NO:2, SEQ ID NO:4, or naturally-occurring amino acid sequences of SEQ ID NO:2 or SEQ ID NO:4. Moreover, such a hypothetical polypeptide would merely be an artifact of a computer predicted translation of a genomic sequence. In any case, it is far more likely that an intron will simply comprise a nonsense sequence which has no open reading frame that it in frame with either exon.

For at least the above reasons, Applicants submit that instant claim 40 does not encompass genomic polynucleotide sequences and, as a result, a description of the genomic sequences related to SEQ ID NO:1 and SEQ ID NO:3 is entirely unnecessary.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 40-42, 46-47, and 52-54 are rejected under 35 U.S.C. § 112, second paragraph, as

allegedly being indefinite with respect to the term "complementary." (Final Office Action, page 14.) Claims 40 and 52, from which claims 41-42, 46-47, and 54 depend, are herein amended to clarify the claimed subject matter by use of the term "fully complementary along its length to." Accordingly, Applicants request withdrawal of the rejection.

Claims 53 and 54 were also rejected as allegedly being vague and indefinite for failing to relate the methods of detection to the target polynucleotide being detected (Final Office Action, page 15). Claims 53 and 54 have been amended to include the phrases "wherein the amount of amplified polynucleotide corresponds to the amount of target polynucleotide in the sample" and "wherein the amount of amplified polynucleotide corresponds to the amount of target polynucleotide in the sample," respectively, to address the rejections.

Utility Rejections under 35 U.S.C. § 101 and § 112, first paragraph

A rejection has been set forth under 35 U.S.C. §101 and §112, first paragraph, based on allegations that "the claimed invention lacks patentable utility due to its not being supported by either [a] specific and/or substantial utility or a well established utility." (Final Office Action, pages 7-12.) The rejection is improper, as the claimed subject matter has a patentable utility as set forth in the instant specification, and a utility well-known to one of ordinary skill in the art.

I. Applicants' invention

The present invention includes, *inter alia*, polynucleotides encoding novel chemokines specifically expressed in the pancreas (PANEC-1 and PANEC-2, referred to collectively as PANEC). PANEC shares a high degree of identity with known chemokines, including but limited to CC-chemokine and monocyte chemoattractant proteins 1, 2, and 3 (MCP-1, MCP-2, and MCP-3). BLAST2 reports based on recently available evidence clearly demonstrate that both PANEC-1 and PANEC-2 (SEQ ID NO:2, Library: 223187 and SEQ ID NO:4, Library:226152, respectively) share up to 100% identity with a number of human leukocyte-specific chemoattractant molecules (see enclosed BLAST2 reports with sequence alignments, Exhibit A). Specifically, SEQ ID NO:1 is 98% identical to several human eotaxins (*e.g.*, g2462478, g1531983, and other). SEQ ID NO:3 is 100% identical to several leukocyte-specific chemokines (*e.g.,* g4128129, g2624925, and others). In fact, *all* of the 30 top BLAST2 hits for each PANEC polypeptide (60 hits in total), are polypeptides that have been characterized as leukocyte-specific chemokines (see enclosed BLAST2 reports without alignments, Exhibit B). Note that CC, MCP, SLP, TCA4, and EBI1, and eotaxin all refer to leukocyte specific chemokines. Applicants submit that one skilled in the art could not reasonably doubt that PANEC-1 and PANEC-2 are leukocyte-specific

chemokines.

II. The use of PANEC or polynucleotides encoding PANEC to attract leukocytes *in vivo* to enhance local immune response is a specific utility under 35 U.S.C. § 101 and § 112, first paragraph

Applicants submit that the invention of the above identified application has real-world utilities based on the specific properties of the disclosed polynucleotides and polypeptides, in addition to utilities as expressed human sequences (see below). Based on the disclosure of PANEC as leukocyte-specific chemokines, and the results of more recent BLAST2 analysis (Exhibits A and B), a practitioner skilled in the art would know how to use the disclosed polynucleotide sequences (including but not limited to the polynucleotides of SEQ ID NO:1 and SEQ ID NO:3) to express leukocyte-specific chemokines (including but not limited to SEQ ID NO:2 and SEQ ID NO:4), isolate and purify the expressed polypeptides, and use the expressed polypeptides for attracting leukocytes to a region of the body in order to direct enhanced local immune response. One skilled in the art would also know how to deliver polynucleotides (including but not limited to SEQ ID NO:1 and SEQ ID NO:3) to target cells *in vivo*, using well known gene therapy delivery techniques (including but not limited to the use of adenovirus and retrovirus delivery vectors). Transduced cells would subsequently express a leukocyte-specific chemokine, resulting in the attraction of leukocytes to target cells and enhanced local immune response.

It is further noted that *leukocyte-specific chemotractants* are chemochemotractants that specifically *target* leukocytes as opposed to chemotractants specifically *expressed* by leukocytes. This distinction is important in view of the comments in the Final Office Action at page 8, lines 13-15:

> Applicants then allege that the claimed invention is a leukocyte-specific chemokine. As noted above the chemokine identity is not supported by sequence identity. Additionally, leukocyte specificity is not supported in that this suggests that PANEC-1 and/or -2 is expressed in leukocytes and not other cell types.

It is apparent that these statements in the Final Office Action are based on the incorrect premise that leukocyte-specific chemotractants are chemochemotractants that specifically target leukocytes. In fact, expression of leukocyte-specific chemokines by pancreatic cells is <u>not</u> inconsistent with Applicants' characterization of the claimed invention. There is experimental evidence for the production of leukocyte-specific chemokine by pancreatic cells. For example, Blanchard *et al.* [(2000) Dig. Dis. Sci. 45:927-32, Reference 1] report that:

> Our studies demonstrate that cells derived from pancreatic ductal epithelium are capable of produding two important cytokines, IL-6 and IL-8, in response to insults that would be reasonably expected to occur in clinical settings. These findings offer important new insights into the pathophysiology of acute pancreatitis. Local production of IL-8, a potent neutrophil

> chemotactic factor, may be the process responsible for the initial infiltration of inflammatory cells in acute pancreatitis. Similarly, local production of IL-6 producing high concentrations in the portal blood may be responsible for the drop in albumin seen in severe acute pancreatitis. Finally, the local production of these and other cytokines may result in the dysfunction or death of endothelial or acinar cells, producing in edema and parenchymal necrosis, the essential features of acute pancreatitis.

Results from Bellone *et al.* [(1999) Am. J. Pathol. 155:537-47, Reference 2] suggest that pancreatic carcinoma solid tumor tissue produces IL-10 and TGF-β. Fink and Norman [(1997) Cytokine 9:1023-1027, Reference 3] conclude that:

> The importance of pro-inflammatory cytokines in the pathogenesis of acute pancreatitis is becoming increasingly apparent. We have demonstrated that IL-1β is produced within the pancreas in a predictable manner which is not model-dependent. Although the link between IL-1β production and the development of pancreatic vacuolization, oedema, inflammation, and eventual acinar necrosis and apoptosis remains to be delineated, accumulating evidence suggests a role for this cytokine family in the development and progression of acute pancreatitis. (Page 1026.)

Taken together, these studies suggest that the controlled, local expression of cytokines can be used to direct or modulate local immune response and that such cytokines are an excellent drugs targets for therapeutic agents designed to prevent excessive or undesirable immune response.

With respect to the utility rejection recited on pages 7-11, the Final Office Action also states that "If applicants supported the leukocyte specificity as well as the chemokine activity function of the instant application, this may overcome these rejections." (Page 11, lines 22-25.) Based on the Specification of the above identified application, the results of recent BLAST2 analysis (which are now of record), and the evidence that pancreatic cells produce cytokines to attract immune cells, Applicants submit that the instant invention has satisfied this requirement. The information of record discloses an invention that has real-world, practical utility both as a cytokines expressed in pancreatic cells and as molecules expressed in human tissues.

Under sections 101 and 112, first paragraph, of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

In the case of the instant application, the rejection fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be withdrawn.

III. Use of polynucleotides encoding PANEC for toxicology testing, drug discovery, and disease diagnosis are additional sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

In addition to the specific utilities described in § II, above, the mere fact that the PANEC-encoding polynucleotides of the instant application are expressed in human tissues (independent of their specific functions as detailed above) immediately implies numerous practical and beneficial uses for the claimed invention in toxicology testing, drug development, and the diagnosis of disease. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

A. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Knowledge of the function of the polypeptide that a polynucleotide encodes is not necessary for the use of the polynucleotide in expression profiling. This fact notwithstanding, the knowledge that a polynucleotide encodes a leukocyte-specific chemokine, as is the case in the instant application, imparts an obvious importance to its expression pattern. For example, the fact that the expression profile of a chemokine is altered in a sample treated with a test compound is highly relevant in assessing the potential side effects of a drug intended to treat human disorders.

Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.,* Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, *et al.*, Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra*.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir *et al.* describes, for example, a Human ToxChip

comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. If the function of a polynucleotide is known, particularly if the function is as important as that of a chemokine, the value of the polynucleotide becomes even more obvious. Using the rapidly evolving gene expression array technologies available to a practitioner, the polynucleotide sequences disclosed in the instant application can readily be put to use, without undue experimentation, to obtain important expression profiling data.

There are numerous uses for the information made possible by expression profiling (some of which are mentioned above). Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and

polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

The rejections should be withdrawn at least because the Office Action failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease.

B. The use of PANEC for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through

expression profiling) are not well-established utilities (which expressly is **not** conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the protein expressed by the claimed nucleic acid or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

1. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § II). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil* Co. v. *Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is **known** to be useful. It is not just a random sequence of speculative use. Because it is expressed in **humans**, a person of ordinary skill in the art would know how to use the claimed polynucleotide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the polynucleotide or the protein it encodes actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of tumor suppressor proteins. Similarly, the claimed invention could be used to determine whether a

specific medical condition, such as leukemia or AIDS, affects the expression of leukocyte-specific chemokines and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed polynucleotide sequences could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein for which it codes: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptide or polynucleotide remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the specific functions of the proteins they encode.

2. A patent applicant may specify a utility that applies to a broad class of inventions

Even if, *arguendo*, the claimed invention encoded a polypeptide that was a member of a broad class of human polypeptides (as the Office Action alleges on page 7, top), the polynucleotides of the instant application would possess substantial utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know

whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions

critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, **all** isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressable (*i.e.,* which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, *e.g.,* for drug discovery purposes. This utility applies to all sequences actually expressed, yet in each case, the utility of the sequence is quite specific, *e.g.,* insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Leukocyte-specific chemokines, like interleukins, GPCRs and fishing rods is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, all of the leukocyte-specific chemokines expressed by humans can be used as tools for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of leukocyte-specific chemokines involved in the recruitment of leukocytes, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless expressed leukocyte-specific chemokines. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

C. Because the use of PANEC in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

The claimed invention's use as a tool for toxicology testing is just such a practical, real-world use. There is no authority for the proposition that use as a tool for research and disease diagnosis is not a substantial utility. In fact, the PTO issues patents for inventions whose only use is to facilitate research,

such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. Perhaps the value of certain polynucleotides in these databases is enhanced by their completeness and/or assigned function; however, each sequence in the database is independently valuable. The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

III. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this procedure. *See* Revised Interim Guidelines at ¶ ¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the case of the instant application, the claims are drawn, *inter alia*, to polynucleotides that encode the leukocyte-specific chemokines PANEC-1 and PANEC-2 (SEQ ID NO:2 and SEQ ID NO:4, respectively). PANEC-1 and PANEC-2 are specifically expressed in the pancreas. The results of BLAST2 reports based on recently available evidence provide overwhelming support of Applicants'

contention that PANEC-1 and PANEC-2 are leukocyte-specific cytokines (see enclosed BLAST2 reports). As leukocyte-specific cytokines, PANEC-1 and PANEC-2 have numerous "real world" utilities as described above.

By ignoring the "reasonable correlation" requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Applicants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Applicants to rebut.

VI. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Junin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training

Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, even broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75). There is no evidence that cells express useless chemokines and no evidence to suggest that polynucleotides encoding PANEC would not be useful in attracting leukocytes to target cells, for toxicological screening, or for drug development.

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

CONCLUSION

For at least the above reasons, it is submitted that the present application is fully in condition for allowance and withdrawal of the outstanding rejections is requested. Early notice to that effect is earnestly solicited. If the Examiner contemplates other actions, or if a telephone conversation would expedite allowance of the claims, the Examiner is invited to contact the undersigned.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The title of the above identified application was amended as follows:

POLYNUCLEOTIDES ENCODING LEUKOCYTE-SPECIFIC [NEW] CHEMOKINES EXPRESSED IN PANCREAS

The paragraph at page 6, lines 8-10, was amended as follows:

Figure [5] 6 shows a relatedness tree of human C-C chemokines. The phylogenetic tree was generated by phylogenetic tree program of DNASTAR software (DNASTAR Inc, Madison WI) using the Clustal method with the PAM250 residue weight table.

IN THE CLAIMS:

Claims 40 and 52-54 have been amended as follows:

40. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide sequence encoding an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4,

b) a polynucleotide sequence encoding a naturally-occurring amino acid sequence which hybridizes under stringent conditions to the full length of a),

c) a polynucleotide sequence [complementary to] fully complementary along its length to a),

d) a polynucleotide sequence [complementary to] fully complementary along its length to b), and

e) a ribonucleotide equivalent of a)-d).

52. An isolated polynucleotide comprising a sequence selected from the group consisting of:

a) a polynucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3,

b) a naturally-occurring polynucleotide sequence which hybridizes under stringent conditions to the full sequence of a),

c) a polynucleotide sequence [complementary to] fully complementary along its length to a),

d) a polynucleotide sequence [complementary to] fully complementary along its length to b), and

e) a ribonucleotide equivalent of a)-d).

53. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 52, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides, said probe comprising a sequence complementary to said target polynucleotide in the sample, and which said probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof; wherein the amount of hybridization complex corresponds to the amount of target polynucleotide in the sample.

54. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 52, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof; wherein the amount of amplified polynucleotide corresponds to the amount of target polynucleotide in the sample.